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# Efficient preparation of imidazo[1,2-*b*]pyridazines under Swern oxidative conditions

Pierre Raboisson, Belew Mekonnen* and Norton P. Peet

*Department of Lead Optimization, ArQule Inc., 19 Presidential Way, Woburn, MA 01801, USA*

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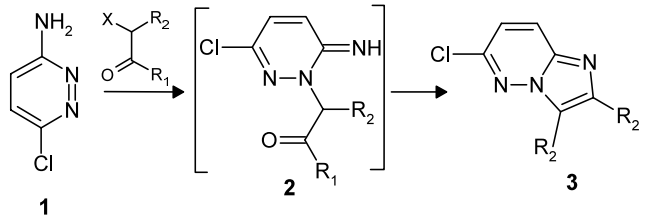
**Abstract**—An efficient synthesis of new imidazo[1,2-*b*]pyridazine derivatives was effected by treating 3,6-dichloropyridazine with various 2-hydroxyethylamines following by imidazole ring formation under Swern oxidative conditions. Some mechanistic aspects of the cyclization step are discussed. © 2003 Published by Elsevier Science Ltd.

Derivatives of imidazo[1,2-*b*]pyridazine are active in a wide spectrum of biological and therapeutic areas.[1–10] The established route for the preparation of imidazo[1,2-*b*]pyridazines **3** involves the condensation of 3-amino-6-chloropyridazine (**1**) with substituted α-halomethylketones in refluxing ethanol (Scheme 1).[10] Thus, α-halo-acetaldehydes would be needed for the synthesis of 3-monosubstituted derivatives. However, these reagents are generally unstable, leading to dehalogenated side products.[9] Moreover, the scarce commercial availability of α-haloacetaldehydes associated with their poor stability limits the scope of this methodology. To the best of our knowledge, only two examples of 3-monosubstituted compounds have been obtained using a cyclocondensation reaction.[9] Recently, direct electrophilic substitution of imidazopyridazine **3a** was found to be a powerful synthetic tool for the preparation of N3 functionalized derivatives.[11,12] This procedure seemed, however, to be limited to a small number of electrophiles.




**Scheme 1.**

Therefore, a need currently exists for an improved method that permits easy and rapid access to a large number of derivatives, especially for applications in parallel synthesis.

In this communication, we report an efficient two-step synthesis of imidazo[1,2-*b*]pyridazines **3a–i** starting from dichloropyridazine **4** and various 2-hydroxyethylamines. The key step in this novel synthetic approach involved an original one-pot tandem cyclization/oxidation reaction under Swern conditions that allows the synthesis of 3-monosubstituted imidazo[1,2-*b*]-pyridazine derivatives which are not available by any other method.

Condensation of dichloropyridazine **4** with various ethanolamines led to monoadducts **5a–i** in 62–91% isolated yields (Scheme 2). Attempts to oxidize alcohol **5b** to the corresponding ketone **6b** using Swern conditions failed and the imidazopyridazine **3b** was surprisingly obtained as the major product in this reaction.[13] The structure of **3b** was unambiguously established using NMR and mass spectral analyses. Similarly, starting from 3-chloro-6-(2-hydroxyethylamino)pyridazine **5a**, imidazopyridazine **3a** was obtained, and was identical in all respects with the product described in the literature.[14] This result could be viewed as the in situ cyclization of the preformed ketone **6**, which can also be obtained by oxidation of **5** with pyridinium dichromate in dimethylformamide.[15]

However, such a mechanism was unlikely since the endocyclic nitrogen of a heterocyclic amidine is reported to be a poor nucleophile toward carbonyl compounds and preferably reacts with alkyl halides or

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* Corresponding author. Tel.: (978) 851 7008; fax: (781) 541 6742; e-mail: bmekonnen@msn.com

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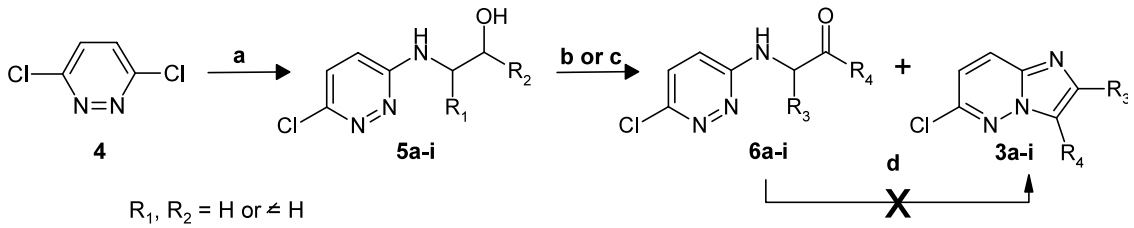
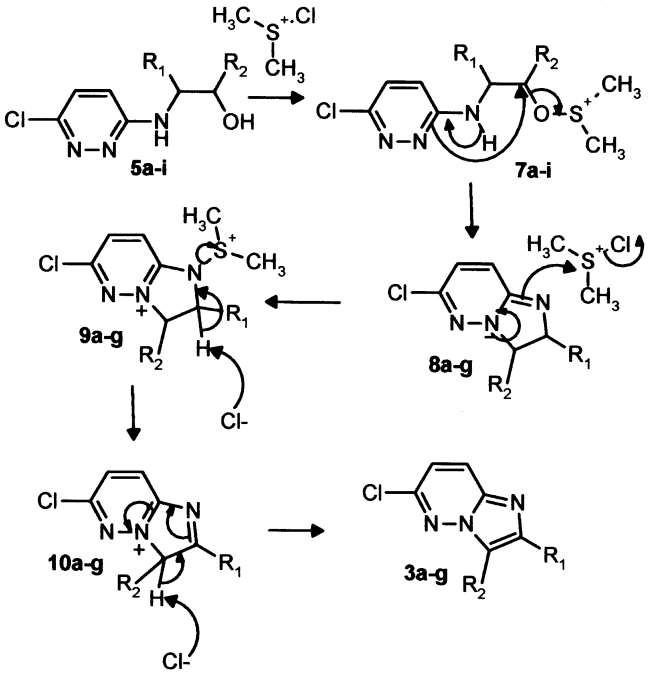



**Scheme 2.** *Reagents and conditions*: (a) $NH_2(R_1)CH(R_2)CHOH$, EtOH, reflux; (b) DMSO, $(COCl)_2$, TEA, $CH_2Cl_2$, −78°C; (c) pyridinium dichromate, DMF, rt; (d) EtOH, reflux.




**Scheme 3.**

Michael acceptors.[9] Moreover, when ketone **6b** was heated in refluxing ethanol, no cyclization product **3b** was obtained. These results suggest that the formation of the imidazole ring may occur through an intramolecular nucleophilic attack of a pyridazine nitrogen onto an activated tetrahedral sulfinium intermediate **7** as depicted in Scheme 3. In this proposed mechanism, the Swern reagent acts as a Lewis acid and generates a highly reactive electrophilic center with a good leaving group, which may lead, after nucleophilic displacement, to imidazolines **8**. The second step, which produced the imidazopyridazines **3**, may involve formation of another *N*-sulfinium intermediate **9**, generated by the attack of the imidazoline **8** onto a second equivalent of chlorodimethylsulfinium ion, followed by a subsequent elimination and deprotonation as shown which leads to the aromatic imidazopyridazines **3**. In support of this proposed mechanism, pure samples of imidazolines **8a** and **8b**, synthesized as previously described,[16] gave under Swern oxidative conditions, the two expected imidazo[1,2-*b*]pyridazines **3a** and **3b**, respectively. In view of these promising results, the scope of this reaction was expanded to other imidazopyridazine derivatives, using a series of 2-hydroxyethylamines. Results are summarized in Table 1. When the reaction was carried out with an activated hydroxyethylamine bearing a heteroatom at position β from the hydroxyl group, the imidazopyridazines **3b–d** were obtained as the sole products. When an inductively electron-donating alkyl group was present, only the ketone **6h** was obtained after treatment with the Swern reagent, which suggests that the intermediate **7h** is probably not nucleophilic enough to be readily cyclized via the intramolecular electrocyclic process. Finally, 3-chloro-6-(2–hydroxy - 3 - methyl - 2 - phenylethylamino)pyridazine (**5g**) led to a mixture of both ketone and imidazopyridazine (**6g** and **3g**, respectively). Interestingly, the more geometrically constrained cyclohexylidene derivative **5f** gave only the cyclic imidazole **3f**. Thus, the competition between the two pathways during the oxidation of the

**Table 1.** Yields of imidazo[1,2-*b*]pyridazines **3** and α-aminoketones **6**[13]

| Compounds **3** and **6** | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Method[a] | Yield ratio **3**/**6** (%)[b] |
|---|---|---|---|---|---|---|
| **a** | H | H | H | H | A | 82/0 |
| **b** | H | $CH_2OPh$ | H | $CH_2OPh$ | A | 84/0 |
| | | | | | B | 0/64 |
| **c** | H | $CH_2OH$ | H | CHO | A | 65/0 |
| **d** | H | $CH_2NH$-*t*-BOC | H | $CH_2NH_2$[c] | A | 68/0 |
| **e** | CHOHPh | H | COPh | H | A | 81/0 |
| **f** | -$(CH_2)_4$- | | -$(CH_2)_4$- | | A | 92/0 |
| **g** | $CH_3$ | Ph | $CH_3$ | Ph | A | 8/81 |
| **h** | H | $CH_3$ | H | $CH_3$ | A | 0/87 |
| **i** | H | Ph | H | Ph | A | 0/81 |

[a] Method A: DMSO, $(COCl)_2$, triethylamine, $CH_2Cl_2$, −78°C→rt; Method B: pyridinium dichromate, DMF, rt.
[b] Represents the ratio of yields of isolated products **3**/**6**.
[c] Compound **3c** was obtained after treatment with trifluoroacetic acid in dichloromethane.

3-chloro-6-(2-hydroxyethylamino) intermediates **5** is not only dependent on inductive effects, which influence the electronic character of the hydroxyl group, but is also highly influenced by geometric parameters.

In summary, we have developed a rapid, practical and efficient procedure for the synthesis of novel 6-chloroimidazo[1,2-*b*]pyridazines **3** via substitution reactions of 3,6-dichloropyridazine (**4**) with various 2-hydroxyethylamines, followed by a tandem cyclization/oxidation reaction under Swern conditions.[13] This methodology represents an efficient procedure for the synthesis of 3-monosubstituted imidazo[1,2-*b*]-pyridazine derivatives which are not available by any other method. Moreover, the chloro group in position 6 of imidazopuridazines would permit access to a large number of 3,6-di- and 2,3,6-tri-substituted derivatives after palladium cross-coupling reactions or nucleophilic displacement of the 6-chloro group.[8,17,18] Furthermore, one of the main advantages of this synthesis is its application to parallel synthesis that permits an easy and rapid access to a large number of derivatives for biological evaluation.

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13. *Typical procedure*: Oxalyl chloride (500 μL, 5.72 mmol) was slowly added under an argon atmosphere at −78°C to a stirred solution of DMSO (610 μL, 8.55 mmol) in dichloromethane (20 mL). After 10 min 3-chloro-6-[(2-hydroxy-3-phenoxy-propyl)amino]pyridazine (**5b**) (800 mg, 2.86 mmol in 2.0 mL of DMSO), which was obtained by condensation of 2-hydroxy-3-phenoxypropylamine and 3,6-dichloropyridazine (**1**) as described earlier,[17] was added and stirring was continued for 20 min at −78°C. Triethylamine (1.7 mL, 12.2 mmol) was added. After 10 min, the reaction mixture was allowed to warm to room temperature, then quenched with isopropanol (5.0 mL). The mixture was diluted with ethyl acetate (200 mL), washed with 2% sodium hypochlorite (200 mL), then with ice-cold water (200 mL), dried ($Na_2SO_4$), and concentrated to dryness under reduced pressure. Chromatography on silica gel (AcOEt) followed by recrystallization from diethyl ether yielded compound **3b** (622 mg, 84%) as colorless crystals: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.45 (s, 2H, $CH_2$), 7.01–7.37 (m, 6H, 6 ArH), 7.91 (s, 1H, 2-H), 7.96 (d, $J=9.3$, 1H, 1 ArH); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 60.3, 116.6, 120.7, 123.1, 126.7, 128.8, 131.1, 136.5, 139.8, 148.8, 159.8. LC–MS: $m/z$, 260 $(M+H)^+$.
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